REMARKS/ARGUMENTS

Upon entry of this amendment, claims 47-54, 56-59, 62 and 67 are pending in this application and are presented for examination. Claims 18-46 have been canceled without prejudice as being directed to a non-elected invention pursuant to a Restriction Requirement. Claims 47 and 62 have been amended. No new matter has been introduced with the foregoing amendments. Reconsideration is respectfully requested.

I. FORMALITIES

Claim 47 has been amended to recite that the method comprises increasing the expression or activity of an ER resident calcium-binding protein in the cell by introducing a polynucleotide operably linked to a promoter into the cell, wherein the polynucleotide encodes the ER resident calcium-binding protein, and wherein the ER resident calcium-binding protein is a member selected from the group consisting of GRP78/BiP, GRP94, GRP72, Calreticulin, Calnexin, Reticulocalbin, Protein disulfide isomerase, cis/trans-Prolyl isomerase, and HSP47. Support for amended claim 47 is found, for example, on page 8, lines 8-11, on page 16, lines 3-23, and in claims as originally filed.

Claim 62 has been amended to recite that the method comprises increasing the expression or activity of an ER resident calcium-binding protein in the cell by administering a pro-inflammatory cytokine to the cell, wherein the pro-inflammatory cytokine is a member selected from the group consisting of interleukin-3 and CSF-1. As previously pointed out, support for amended claim 62 is found, for example, on page 17, lines 1-4. The reference cited therein, Brewer *et al.*, *EMBO J.*, 16:7207-7216 (1997), discloses that IL-3 and colony stimulating factor-1 (CSF-1) induce the expression of ER resident calcium-binding proteins. Applicants submit that prior to the filing of the instant application, it was well known in the art that both IL-3 and CSF-1 are pro-inflammatory cytokines (*see, e.g.,* Yun *et al.*, *Life Sci.*, 67:2855-2863 (2000); abstract) that are useful for inducing the expression of ER resident calcium-binding proteins.

Thus, no new matter has been introduced. As such, Applicants respectfully request that the amended claims be entered.

II. OBJECTION TO THE DRAWINGS

As previously indicated and as acknowledged by the Examiner in the Office Action, Applicants will file formal drawings upon receiving a Notice of Allowance.

III. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH: ENABLEMENT

Claims 47-54, 56-59, 62 and 67 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with the claims. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

As explained above, in order to expedite prosecution of the present case, Applicants have amended claim 47 to recite a method of inhibiting the generation of active thrombin on the surface of a cell within an atherosclerotic plaque within a mammal comprising increasing the expression or activity of an ER resident calcium-binding protein in the cell by introducing a polynucleotide operably linked to a promoter into the cell, wherein the polynucleotide encodes the ER resident calcium-binding protein, ***and wherein the ER resident calcium-binding protein is a member selected from the group consisting of GRP78/BiP, GRP94, GRP72, Calreticulin, Calnexin, Reticulocalbin, Protein disulfide isomerase, cis/trans-Prolyl isomerase, and HSP47***. As presently amended, claim 47 does not encompass administering any compound that activates or increases the level or expression of any ER resident chaperone protein, but instead encompasses the introduction of a polynucleotide encoding a specific list of ER resident calcium-binding protein into the cell. Applicants submit that the application, at the time of filing, contained sufficient information so as to enable one of skill in the art to make and use the claimed invention ***without*** undue experimentation. In particular, the instant specification teaches that increasing the expression or activity of ER

resident calcium-binding proteins such as GRP78/BiP, GRP94, reticulocalbin, calreticulin, and calnexin can be used to inhibit the generation of active thrombin on the surface of a cell (*see,* page 8, lines 3-11 and page 16, lines 3-23). As such, it is readily apparent that the instant specification enables the full scope of amended claim 47 and, thus, undue experimentation is ***not*** required to practice the full scope of the claim. In view of the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph, rejection.

The Examiner continues to allege that because Dai *et al.*, *Arteriosclerosis, Thrombosis, and Vascular Biology*, 17:2359-2368 (1997) ("Dai *et al.*") disclose that the calcium-binding protein calsequestrin does not decrease plaque area, "additional experimentation is required in order to determine which calcium decreasing molecules would work in the claimed methods and which would not work." In response, Applicants respectfully point out that calsequestrin is ***not*** an ER resident calcium-binding protein. Rather, calsequestrin is a calcium-binding protein residing in the sarcoplasmic reticulum (SR) that is responsible for maintaining the level of intracellular calcium in cardiac and skeletal muscle by storing and releasing calcium. As the ER and SR are clearly distinct intracellular compartments performing distinct functions, *e.g.,* the ER being involved in the secretory pathway and the SR being involved in muscle contractility, Applicants assert that calsequestrin is not within the scope of amended claim 47, which recites that the polynucleotide encodes an ***ER resident*** calcium-binding protein, ***wherein the ER resident calcium-binding protein is a member selected from the group consisting of GRP78/BiP, GRP94, GRP72, Calreticulin, Calnexin, Reticulocalbin, Protein disulfide isomerase, cis/trans-Prolyl isomerase, and HSP47.*** As such, undue experimentation would ***not*** be required to practice the full scope of the claim. In view of the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph rejection.

Finally, the Examiner continues to raise some concern about the administration of the nucleic acid of interest to the target cell. However, as previously explained, the specification teaches a number of delivery methods for introducing the nucleic acid to the target cell. Such methods include, but are not limited to, the use of both viral vectors and non-viral vectors. For the latter, the specification teaches that such non-viral vectors are typically introduced into cells

either as naked DNA or in combination with various transfection-facilitating agents. The specification provides numerous examples of liposome-mediated transfection-facilitating agents (*e.g.*, cationic liposomes, immunoliposomes, other lipid-based carriers, *etc.*) that were known to and used by those of skill in the art as of the filing date to deliver nucleic acid to target cells of interest. Moreover, Applicants respectfully submit that, as of the filing date, it was well within the level of skill in the art to be able to adjust the dosing regime so that the vector of interest expresses the therapeutic compound at a high enough level and for a sufficient amount of time to have a therapeutic effect. As such, Applicants assert that the teachings of the instant specification, coupled with the general knowledge in the art at the time of the present invention, provide modes of delivery that allow for administration of nucleic acids to target cells. Thus, undue experimentation would ***not*** be needed to carry out the methods of the present invention. In view of the foregoing, Applicants respectfully request that the Examiner withdraw the 35 U.S.C. § 112, first paragraph, rejection.

IV. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH: WRITTEN DESCRIPTION

Claims 62 and 67 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. In support of this rejection, the Examiner states that "although the specification has support for the specific pro-inflammatory cytokines IL-3 and CSF-1, the specification does not have support for the whole genus of "pro-inflammatory cytokines" (*see*, page 6 of the Office Action).

In order to expedite prosecution, claim 62 has been amended to recite that the method comprises increasing the expression or activity of an ER resident calcium-binding protein in the cell by administering a pro-inflammatory cytokine to the cell, wherein the pro-inflammatory cytokine is a member selected from the group consisting of interleukin-3 and CSF-1. In view of the amendment to claim 62 and, in turn, dependent claim 67, the Examiner's rejection is rendered moot. Accordingly, Applicants respectfully request that the Examiner withdraw this § 112, first paragraph, rejection.

V. REJECTION UNDER 35 U.S.C. § 102(b): Hansson *et al.*

Claim 62 has been rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,208,019 ("Hansson *et al.*"). In particular, the Examiner alleges that the claims "encompass a method wherein the expression of an ER resident calcium binding protein is increased by administration of a pro-inflammatory cytokine in a cell," that "Hansson *et al.* teach a method wherein gamma-interferon is administered to an animal model for inhibiting the growth of cells in intimal lesions as well as in atherosclerosis," and that "interferon gamma was known in the prior art. . . as a 'pro-inflammatory cytokine" (*see*, page 7 of the Office Action). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

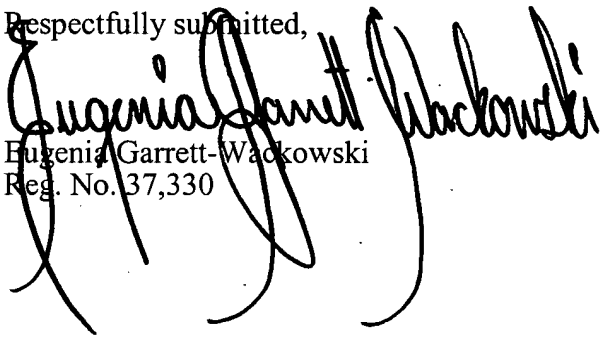
As previously explained, in order to expedite prosecution, claim 62 has been amended to recite that the method comprises increasing the expression or activity of an ER resident calcium-binding protein in the cell by administering a pro-inflammatory cytokine to the cell, wherein the pro-inflammatory cytokine is a member selected from the group consisting of interleukin-3 and CSF-1. In view of the amendment to claim 62 and, in turn, dependent claim 67, the Examiner's rejection is rendered moot. Accordingly, Applicants respectfully request that the Examiner withdraw this § 102(b) rejection.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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